REFORMING DRUG APPROVAL IN THE UNITED STATES: MEASURES NECESSARY TO ALLEVIATE THE CASH CRUNCH FACED BY SMALL BIOTECHNOLOGY COMPANIES

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I. INTRODUCTION

Over the past decade, the infant biotechnology industry, led by small biotechnology companies, has produced numerous breakthrough drugs which have saved lives, reduced suffering and cut the cost of health care. Given that the biopharmaceutical industry has only been in existence for a little over 20 years, biotechnology holds enormous potential for the advancement of medical treatments. Unfortunately, even with biotechnology, as with the more traditional methods of drug development, the government mandated testing and approval of new therapeutic products takes a considerable amount of time and costs an exorbitant amount of money. The United States has the most demanding drug approval process in the world. Under the current Food and Drug Administra-

tion's drug approval process, the time required to gain approval for new drugs averages between 10 to 12 years and the cost approximates $350 million.[1] In addition, the Food and Drug Administration (FDA) has come under attack as taking too conservative of an approach to approving beneficial new drugs.

The purpose of this paper is to analyze the effects of this costly drug approval process on small biotechnology companies, to determine the effects of a decline in small biotechnology companies on the United States and to analyze current proposals

to change the current Food and Drug Administration's drug approval process to ensure the survival of small biotechnology companies.

Part II of this paper identifies the various stages of the drug approval process. Part III explores the policy behind the FDA's extensive drug approval process. Part IV examines the adverse affects of the drug approval process on small biotechnology companies. Part V analyzes the effect of a declining biotechnology industry on the United States. Part VI addresses current proposals to change the FDA drug approval process focusing on their ability to help small biotechnology companies.

II. FDA DRUG APPROVAL PROCESS

The Federal Food, Drug and Cosmetic Act of 1938 amended by the Drug

[1]The Changing Environment for US. Pharmaceuticals, THE BOSTON CONSULTING GROUP, Apr. 1993; See also Joan C. Hamilton et al., Biotech. America's Dream Machine, BUS. WK., Mar. 2, 1992, at 66; David Hanson, Pharmaceutical Industry Optimistic About Improvements at FDA, CHEM & ENG NEWS, Jan. 27, 1992, at 28.

Amendments of 1962 regulates the approval of new drugs in the United States.[2] Under the current regime, before a drug sponsor may market a drug in interstate commerce, the FDA must approve the drug as safe and effective.[3] Before the FDA will approve a drug as safe and effective, the drug must undergo rigorous testing procedures which are extremely time consuming and costly.

A. Pre-Clinical Testing

In pre-clinical testing, a new drug sponsor must conduct initial investigations of the drug though extensive tests on laboratory animals. For example, the FDA requires 12 months of toxicity tests in 2 species of laboratory animals.[4] This initial testing is conducted to ensure that the new drug is reasonably safe for clinical trials and has the potential to treat a specific disease.[5] This first stage of testing takes approximately 3.5 years.[6]

B. Notice of Claimed Investigational Exemption for a New Drug

If the pre-clinical investigations and animal testing indicate that

[2]The biologics Act of 1902 imposes additional requirements on biologics which include many of the drugs produced by biotechnology companies. For example, biologics must be produced in alicensed facility while drugs not classified as biologics simply must be manufactured by good manufacturing practices. *See* Peter B. Hutt and Richard A. Merrill, FOOD AND DRUG LAW (1991). Also, biologics are reviewed by a different center in the FDA than traditional drugs. *Id* Despite these differences, biologics and drugs are subject to the same general approval process with the same structure of pre-clinical and clinical trials. For purposes of this paper, the differences in regulation will be immaterial and I will treat traditional chemically-derived drugs and biotechnology-derived drugs as being subject to the same regulatory procedure.

[3]J. Nielsen, HANDBOOK OF FEDERAL DRUG LAW 14 (1986).

[4]John Patrick Dillman, *Prescription Drug Approval and Terminal Diseases. Desperate Times Require Desperate Measures; 44* VAND. L. REv. 925, 928 (1991).

[5]*1d.* at 928.

[6]Veronica Henry, *Problems with Pharmaceutical Regulation in the United States,* 14 J. LEGAL MED. 617 (1993).

the drug is reasonably safe for human clinical trials and has the potential to treat a specific disease, the drug sponsor may file a Notice of Claimed Investigational Exemption for a New Drug (IND) with the FDA.[7] The IND notice must contain the name of the drug, active ingredients, pharmacological class, structural formula, route of administration, and a summary of the pharmacological and toxicological effects of the drug and the pharmacokinetics and biologic disposition in animals.[8] In addition to summarizing the scientific data, the IND outlines the plans for clinical trials.[9] Clinical studies on human beings may commence 30 days after the FDA receives the IND notice unless the FDA objects.[10] The FDA may put a clinical hold on an IND during the initial 30 day period if the FDA deems the application to be deficient in any manner.[11] The key concerns of the FDA in reviewing the IND are: (1) Adequate protection of the human test subjects, (2) Informed consent of the human test subjects; and (3) A well designed study so that essential information can be obtained. [12]

C. Human Testing

Clinical trials in human beings occur in three phases. In Phase I, the drug sponsor introduces the drug into a small group (usually between 20 and 100) of healthy human volunteers for a short period of time.[13] Phase I testing focuses

[7]. Nielsen, *supra* note 3 at 14.

[8]Henry *supra* note 6 at 619.

[9]GAO REPORTS, *FDA User Fees – Current Measures not Sufficient for Evaluating Effect on Public Health,* Aug. 1, 1994 at 10.

[10] *1d*

[11]

[12]Food and Drug Agency Commissioner David A. Kessler, M.D., Address at 92nd Street Y in New York City, N.Y. (Jan. 7, 1993).

[13]Henry,supranote6 at619; *See also* 21 C.F.R. x 312.21(a)(1990).

primarily on drug safety.[14] The drug sponsor also evaluates other factors, such as rates of metabolism, absorption, and elimination.[15] Apparently, the FDA uses Phase I to prevent toxic compounds from reaching large groups of people.

In Phase II, the drug sponsor first administers the drug to subjects who have the specific disease or symptoms for which the drug is intended.[16] Phase II testing monitors drug safety in a larger population than Phase I testing (usually between 100 to 300).[17] The purpose of Phase II is to develop dosage and toxicity data and to obtain preliminary evidence of efficacy.[18] Phase II testing is a crucial part of the testing process because the results indicate whether the drug has any real promise for treating the condition in question. Phase II lasts about 2 years and consists primarily of placebo-controlled or dose comparison, double-blind, randomized studies.[19]

Phase III testing usually is the final test for a drug's safety and effectiveness. Phase III studies are conducted only after the effectiveness of the drug has been evidenced through Phase I and Phase II clinical trials.[20] These studies usually involve approximately 1000 to 3000 patients and are often placebo-controlled or compared with standard therapies.[21] The purpose of Phase III studies is to gather additional information about the drug's safety and effectiveness which is needed to evaluate the risks and benefits of the drug. Phase III studies usually

[14] 21 C.F.R. x 312.21(a) (1990).
[15] *Id*
[16] 2, C.F.R. §312.21(b) (1993).
[17] Henry, *supra* note 6 at 619.
[18] *Id*
[19] *Id.*
[20] 21 C.F.R. x 3 12.21(c) (1993).
[21] Henry *supra* note 6 at 620.

last about 3 years.[22]

Sometimes the FDA adds a fourth phase that resembles post-marketing surveillance.[23] During Phase IV, the FDA can re-evaluate its earlier approval and demand either a recall or re-labeling.[24] Currently, the FDA makes little use of Phase IV surveillance.

D. New **Drug Application**

After the drug manufacturer successfully completes all IND clinical testing and the results indicate that the drug is safe and effective, the drug manufacturer may file a New Drug Application (NDA) (or a Product License Application for biologics) with the FDA.[25] The NDA contains information about test results, chemical composition, manufacturing methods, proposed labeling, safety, effectiveness, and other relevant data.[26] The NDA may be thousands of pages long.[27] Once the NDA is received, the FDA has 60 days to determine whether the NDA will be officially filed.[28] If the FDA finds that the NDA is sufficiently complete to permit a substantive review, it may file and continue to review it.[29] If the FDA finds that the NDA is not sufficiently complete to permit a substantive

[22] *Id*
[23] ABA: Aids Coordinating Committee, AIDS: THE LEGAL ISsUES 139, 141 (1988).
[24] *1d* at 142.
[25] 21 U.S.C.A. x 355 (b)(1)(A) (1972 & Supp. 1993).
[26] Henry *supra* note 6 at 621.
[27] Dillman *supra* note 4 at 930.
[28] GA0 REPORTS, *supra* note 9 at 12.
[29] *Id*

review, the agency may refuse to file the application.[30] If the FDA refuses to file the NDA, review of the NDA may not continue.[31] The drug sponsor may then meet with the FDA to discuss the agency's grounds for refusing to file the NDA and may insist that the NDA be filed over protest.[32] Once the NDA is filed, the FDA's review of the NDA takes approximately 20 months.[33] **III. POLICY BEHIND STRINGENT DRUG APPROVAL PROCESS: HISTORY OF DRUG REGULATION IN THE UNITED STATES**

The objective behind the FDA drug approval process is the protection of United States citizens by ensuring that only safe and effective drugs reach the marketplace. Therefore, the FDA regulatory system is set up to ensure that all drugs brought to the market are safe, or in other words, present therapeutic benefits which outweigh their risks to health. Furthermore, all drugs marketed must be effective so that individuals do not treat an illness with an ineffective drug. To understand the development of such an extensive system of drug approval in the United States, it is necessary to review the history of drug regulation in the United States.

Federal regulation of drugs and biologics commenced with the Vaccine Act of 1913 (the Act) which was passed following the development of a small pox

[30] *ld*
[31]
[32] *Id*
[33] Lisa Piercey, *FDA Review Times, Approvals Are Down,* BIo WORLD TODAY, Jan. 19, 1995 at 1.

vaccine.[34] The Act authorized the President to appoint an agent of the Federal government to preserve the vaccine and to furnish it to United States citizens.[35] Following an outbreak of small pox in North Carolina caused by a vaccine furnished by the Federal small pox agent, Congress repealed the Act concluding that the vaccine's regulation should be the responsibility of local authorities.[36]

The Biologics Act of 1902 was enacted as a response to the use of contaminated vaccine which lead to several health crises.[37] For example, in 1902, several children died in St. Louis from an outbreak of tetanus which was traced to

PHARMACOLOGY AND ThERAPEUTICS 537, 53 8-539. contaminated diphtheria antitoxin.[38] The Biologics Act required, as it does today, product and establishment licensure for biologics.[39]

No similar tragedy preceded the Pure Food and Drugs Act of 1906 which made it a criminal offense to misbrand or adulterate a drug.[40] As a result, the statute required no pre-market approval. However, tragedy struck in 1937 increasing the demand for pre-market governmental scrutiny of a drug's safety.

[34]Peter B. Hutt and Richard A. Merrill, FOOD AND DRUG LAW 476-480 (1991); Peter Barton Hutt, *Investigations and Reports Respecting FDA Regulation of New Drugs,* 33 CLINICAL

[35]*Id*

[36]*Id*

[37]*Id*

[38]*Id*

[39]*Id*

[40]Pure Food and Drug Act of 1906, ch. 3915, xx 1-13, 34 Stat. 768, repealed by Federal Food, Drug, and Cosmetic Act of 1938, ch. 675, x 902(a), 52 Stat. 1040, 1059 (codified as amended at 21 U.S.C. x 301 (1988)).

At least 73 people died as a result of ingesting a drug called Elixir Sulfanilamide which was prepared by the Massengill Company.[41] In 1938, Congress passed the Federal Food, Drug and Cosmetic Act of 1938 (the 1938 Act) which created pre-market notification.[42] The 1938 Act required a drug manufacturer to submit an application for marketing approval of a new drug.[43] The FDA could reject the application, but if the FDA did not act within 60 days the drug could be marketed.[44] The 1938 Act provided the FDA with the ability to screen new drugs for safety while allowing most new drugs quick access to the market.

In the early 1960's, the thalidomide drug tragedy in Europe dispelled any arguments for quick disbursement of drugs. The tragedy resulted from a tranquilizer called thalidomide which caused approximately 8000 birth defects in Europe.[45] Although the United States escaped this tragedy because the FDA had not allowed the NDA for thalidomide to become effective, Congress amended the 1938 Act to strengthen control over the distribution of new drugs.[46] The Drug Amendments of 1962 amended section *505* of the 1938 Act to require proof of safety and effectiveness before approval of a drug. As a result, the FDA gained substantial power and discretion to affect the drug approval process as illustrated by the current drug approval process.

IV. DETRIMENTAL EFFECT ON SMALL BIOTECHNOLOGY

[41] *5ee* Peter B. Hutt & Richard A. Merrill, FOOD AND DRUG LAW 476 (1991).

[42] Federal Food, Drug and Cosmetic Act of 1938, ch. 675, x 501, 52 Stat. 1040, 1049 (codified as amended at 21 U.S.C. x 351 (1988)) [herein 1938 Act].

[43] 1938 Act, 21 U.S.C. x 355 (1988)

[44] 1938 Act, 21 U.S.C. x 255(c) (1988).

[45] Harvey Teff, *Drug Approval in England and the United States,* 33 A.M. J. COMP. L. 567 (1985).

[46] Hutt and Merrill *supra* note 34; Hutt *supra* note 34.

COMPANIES

The approximate 1300 small biotechnology companies in the United States, all less than 20 years old,[47]seeking to use cutting edge genetic or other technologies to create new drugs and health products, perform a substantial amount of the United States' drug research.[48] Approximately two dozen biotechnology-derived drugs have entered the United States market.[49] About 150 more are in the Investigational stage.[50] According to the Boston Consulting Group, an average of one-third of all pharmaceutical research is based on molecular biology.[51]

Nearly all of these biotechnology companies have no current profits nor products. Funding of biotechnology companies is based on the belief that these companies will produce the world's future drugs which in turn will generate

[47]Cheryl D. Hardy, *Patent Protection and Raw Materials. The Convention on Biological Diversity and its Implications for US. Policy on the Development and Commercialization of Biotechnology*, 15 U. PA. J. INT'L BUS. L 299, 300.

[48]*5ee* John Eckhouse, *Biotechnology Industry is Poised for Recovery. New Drugs Making it to Market Sooner,* SAN FRANCISCO CHRONICLE, Oct. 7, 1994 at B 1.

[49]Charles Marwick, *Biotechnology Industry Calls for Active US Role; Medical News Perspectives,* 271 JAMA 648, 649 (1994). An example is Amgen, Inc.'s drug Epogen, which treats anemia in endstage renal disease patients. *See* Hardy *supra* note 48 at 301. Other promising biotechnology products have entered the United States market including treatment for the side effects of chemotherapy, growth deficiencies in children, heart attacks and AIDS related anemia. *Id*

[50]Marwick *supra* note 50 at 649.

[51]Laurie Lewis, *Manufacturers are Under Continuing Pressure to Reduce Prices, to Improve Profitability,* 12 BUSINESS AND HEALTH 23, 25 (1994). Therefore, the fact that only 1 out of 22 new drugs approved in 1994 was derived from biotechnology and that in 1993 only 4 out of 25 were derived from biotechnology is misleading in evaluating the role of biotechnology in future drug development. The infancy of biotechnology as a means to produce drugs combined with the length of time required for drug approval has limited the number of biotechnology-derived drugs that have reached the stage where they could be approved. Furthermore, it may be a sign that the FDA has been too conservative in approving biotechnology-derived drugs.

millions of dollars. However, the current drug regulatory scheme threatens the existence of these small biotechnology companies. First, the extreme cost of FDA drug approval increases the funding requirements of small biotechnology companies and decreases investor's willingness to invest in these companies. Second, the FDA's politically conservative approach to drug approval decreases the chance that safe and effective drugs will be approved effectively penalizing small biotechnology companies. These two problems have created a cash crunch for small biotechnology companies which likely will result in a reduction in the number of such companies in the future.

A. Extreme Cost of FDA Drug Approval

The extreme cost of the FDA drug approval process has created a perpetual cycle of capitalization problems for small biotechnology companies: (1) The high cost of drug approval combined with a small biotechnology company's limited financial resources limits the number of products that a biotechnology company can develop and decreases the probability that a biotechnology company will be able to survive the lengthy drug approval process; (2) Investors will not invest because of the substantial risk associated with biotechnology companies due to their reliance on a few products and due to the likelihood that a product will never be approved; and (3) Investor's unwillingness to invest in biotechnology increases the financing problems of biotechnology companies.

The process of drug development takes approximately 10 to 12 years and costs approximately $350 million.[52] Biotechnology companies burn considerable amounts of cash each month and generate no profits.. For example, in 1992, the average biotechnology company burned $664,000 a month.[53] This enormous burn rate, attributable to each drug run through the FDA drug approval process, limits the amount of potential new drugs that may be pursued in the laboratory and in clinical trials by these small biotechnology companies. Therefore, small biotechnology companies base their success or failure on a few drugs getting to market. Consequently, a failure of a drug in clinical tests greatly devalues the company resulting in a substantial loss to investors.[54]

[52] *The Changing Environment for US. Pharmaceuticals,* THE BOSTON CONSULTING GROUP, Apr. 1993; *See also* Joan C. Hamilton et al., *Biotech: America˜ Dream Machine,* BUS. WK., Mar. 2, 1992, at 66; David Hanson, *Pharmaceutical Industry Optimistic About Improvements at FDA,* CHEM& ENG NEWS, Jan. 27, 1992, at 28.

[53] Sandra Sugawara, *Biotech Firms Forming More Strategic Links: Young Industry Seeks Support from Mature Corporations,* THE WASHINGTON POST, October 19, 1992 at fi.

[54] The history of MedImmune, luc, a biotechnology company who has no current products nor profits is illustrative of the risk associated with investing in biotechnology companies that rely on a limited number of experimental drugs. In July 1994, MedImmune, Inc.'s stock price closed at $4.87, down from a peak of $32.62 on November 1993. Stan Hinden, *Washington Investing: Lacking a Cure, MedImmune Saw its Stock Sicken,* THE WASHINGTON POST, August 1, 1994 at f25. The dramatic decline in the company's stock over this 10 month time period can be attributed to the company's problems with the FDA approval of RespiGam, an experimental drug designed to battle a respiratory virus that kills 4500 infants a year. *Id* In November 1993, MedImmune completed its clinical tests on RespiGam as a potential treatment for the virus and brought its results before an FDA panel. *Id* However, FDA denied approval of the drug stating that more testing was necessary because mistakes were made in the methods used in the three year study of the 249 children. *Id* After FDA disapproval, the stock plummeted to $11.50 per share. *Id* The price of the stock plummeted further upon MedImmune's announcement in July 1994 that the company would not pursue further clinical tests of RespiGam. *Id*

ProCyte Corp., a biotech company in Kirkland, Washington is another example of the reality of risky, long-term research and development projects. In October 1994, ProCyte Corp. revealed that its breakthrough Lamin gel drug was not effective in treating diabetic foot ulcers. Ronald E. Yates, *Cash Crunch: Pushing Biotech Firms to Mortgage Technology,* CHICAGO TRIBUNE, October 23, 1994 at 2. This revelation triggered a plunge in the stock price from $6.12 to $2.37. *Id*

In the same month, Gensia Pharmaceuticals Inc., a San Diego biotech company, released poor results of a clinical trial of its heart-surgery drug, Protara. *Id* Protara was supposed to reduce the risk of heart attacks in bypass patients. *Id* However, the drug performed no better than a placebo in clinical tests. *Id* Gensia's stock plunged from over $10 per share to $4.62. *Id*

As a result, investors have become unwilling to invest in such risky ventures[55] which has left biotechnology companies scrambling for precious financing for drug research. **B. Politically Conservative FDA**

Political influence on the FDA has caused the FDA to take an extremely conservative approach to drug approval. The FDA does not base new drug approval decisions by objectively weighing the benefits of a new drug against its potential costs. Rather, the FDA has taken the position that when the slightest doubt exists about a drug's potential harm the drug should not be approved even in the face of substantial evidence of the new drug's potential benefits. Business Week in its January 30, 1995 issue illustrated the FDA's conservative approach to drug approval by reviewing Merck & Co.'s lack of success in getting Varivax, a chicken pox vaccine, approved.

To some critics, nothing demonstrates FDA foot-dragging better than the chicken pox vaccine Varivax. Since 1981, this vaccine has been tested safely on more than 10,000 people in the U.S. Since 1984, 2 million children in Europe and Asia have had versions of it. Yet Varivax is still lumbering through the FDA. An FDA advisory committee first recommended approval in January, 1990, a year after Merck & Co. sought the OK. Early last year, a second panel pronounced Varivax safe and effective. The Centers for Disease Control (CDC) and the

[55] *5ee* Marwick *supra* note 48. For example, the amount of money raised through initial public offerings by biotechnology companies dropped from $33 million in 1991 to $22 million in 1993. *Id* at 648. The total amount of money raised by biotechnology companies dropped form $3.4 billion in 1991 to $2.8 billion in 1993. *Id*

American Academy of Pediatrics both urge universal use

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Yet the FDA is unapologetic about its tough stance. Data from 20 years' experience in Japan and elsewhere show that as many as 2% of inoculated children develop mild cases of chicken pox, a higher failure rate than other childhood inoculations. Regulators also worry that – years later – Varivax might spawn adult cases of the disease or trigger related viral conditions, such as shingles.[56] Two reasons lie behind the FDA's conservative approach to drug approval. First, Congress controls the FDA through various devices and therefore controls U.S. drug policy. Second, forces opposed to the introduction of new drugs have a greater influence on Congress than those that favor the introduction of new drugs.

Congress mandates FDA drug approval policy through the use of Congressional oversight committees which conduct rigorous hearings regarding FDA policy. Since the passage of the Kefauver-Harris Amendment, the FDA has been subject to almost continuous hearings from a number of well known Congressmen, including Representatives Fountain and Rodgers and Senators Kefauver, Kennedy and Nelson.[57] Thus, the Commissioner of the FDA is subject to hostile Congressional hearings when the FDA deviates from Congression-

[56]John Carey, Joseph Weber and Joan O'C. Hamilton, *Is the FDA Hooked on Caution,* BUSINESS WEEK, Jan 30, 1995. at 73. However, it must be noted that the FDA approved Varivax on March 17, 1995. BNA HEALTH CARE DAILY, *FDA Approval. Vaccines to be Available in 8 Weeks,* March 23, 1995. However, this unexpected approval of the vaccine does not minimize the tremendous amount of unnecessary time spent on reviewing this drug especially given that the drug was recommended for approval by two independent advisory groups years before its FDA approval.

[57]Frederick Beckner III, *The FDA 's War on Drugs,* 82 GEO. L. J. 529, 544 (1993).

ally acceptable drug approval policy.[58] Such pressure from Congress inevitably shapes the FDA's drug policy.

Forces that oppose less drug regulation have more influence on Congress than forces in favor of less regulation. Consumer groups opposed to less regulation of new drugs have engineered a considerable following and maintain substantial influence in Congress.[59] These groups have used past drug tragedies as their rallying cry. Deaths and deformities are vivid tangible results of less regulation. These images compel membership by generating a fear of less regulation and by creating a sense of moral duty to oppose less regulation. No Congressman wants to say to his constituents that he was a responsible participant in a governmental system that approved a thalidomide-type drug which causes 1000's of birth defects.

Forces in favor of less regulation have had a tougher time generating support for their cause.[60] First, drug consumers have little incentive to join groups to petition for less regulation. The drug lag does not result in vivid harms which can be used as a source of an emotional rallying cry. Also, the benefits derived from less regulation are dispersed throughout country and therefore a free rider

[58] *5ee Id* For example, in May 1969, the FDA decertified the drug Panalba by a summary procedure without a prior hearing. UpJohn, the maker of the drug used its ties to the Nixon Administration to get Health, Education, and Welfare Secretary Robert Finch to order the FDA to grant a hearing. When word of the intervention leaked to Congress, however, pressure was quickly brought to bear on the FDA. The order to grant a hearing was reversed within a day of being brought, and the President was forced to endure an embarrassing public hearing. *Id* at 543-544.

[59] *Id*

[60] *Id*

problem exists.[61] Second, while the biotechnology industry has pushed hard for less regulations, the drug industry as a whole does not share the same interests with regard to the drug review process. Large drug companies benefit from a stringent drug approval process because it serves as a barrier to entry to the small firms. Less regulation simply means more competition for the large firms.

Congressional control of the FDA and public sentiment against less regulation have lead to the FDA's conservative approach to drug approval. Congressional pressure on the FDA discouraging approval of potentially harmful drugs may be described as intense.[62] Countless Congressional hearings have been conducted to criticize the approval of new drugs.[63] Meanwhile, no hearing has been conducted to investigate the failure of the FDA to approve new drugs.[64] Former FDA Commissioner Alexander Schmidt summarized the current influence of Congress on the FDA:

When it comes to pure unadulterated and directly applied pressure on the FDA, the industry can't hold a candle to Congress. .. By far the greatest pressure that the Bureau of Drugs or the Food and Drug Administration receives with respect to the new drug approval process is brought to bear through Congressional hearings... The message to the FDA could not be clearer. Whenever

[61] *1d* at 547-549.

[62] Peter Barton Hutt, *Investigations and Reports Respecting FDA Regulation of New Drugs,* 33 CLINICAL PHARMACOLOGY AND THERAPEUTICS 537, 674.

[63] *Id*

[64] *5ee Id* For example, Dr. Frances 0. Kelsey received the Presidential Award of Distinguished Federal Civilian Service from President John F. Kennedy for refusing to approve Thalidomide. *Id* at538. However, it is unlikely that any such award would be granted to an FDA official who approved a safe and effective drug.

a controversy over a new drug is resolved by its approval, the Agency and the individuals involved likely will be investigated. Whenever such a drug is disapproved, no inquiry will be made. The Congressional pressure for our negative action is.

intense.[65]

As a result, the FDA is obsessed with minimizing risk keeping products off of the market for years.

Not only has the FDA refused to approve drugs due to over caution against the potential harms produced by new drugs. The FDA has also refused to approve drugs based on politically motivated moral judgments. For example, RU-486, a drug used as an abortifacient, is scientifically beneficial in that its benefits outweigh its risks.[66] However, while countries such as Great Britain have approved RU-486, the FDA has banned its importation. The reason for such a ban appears to be purely political – the drug is used to cause abortions. In other words, the FDA has played policy maker rather than the scientific evaluator of new drugs.[67] Such a systematic bias against the approval of drugs

[65] Beckner *supra* note 57 at 546.

[66] *5ee* Claire L. Ahem, *Drug Approval in the United States and England. A Question of Medical Safety or Moral Persuasion?,* 17 SUFFOLK TRANSNATIONAL LAW REVIEW 93 (1994).

[67] 1t is also possible that politics could influence the FDA to approve drugs which do not have scientific merit. For example, in the instance of AIDS patients who are crying out for any new drug. However, this situation is apparently rarer. Furthermore, applying a scientific costlbenefit analysis to all new drugs does not mean that experimental drugs for diseases such as AIDS should not be allowed into the market before their effectiveness and safety have been adequately revealed. Rather, this scientific method merely requires that the expected benefits of the drug be weighed against the cost of the drug not being available which is often quite high given the seriousness of AIDS. Furthermore, an unpolitical scientific method is superior in getting such drugs to market quicker because such a method would not limit

compounds the problems faced by biotechnology companies. This bias reduces the likelihood that a drug will be approved even if the product is scientifically beneficial.[68] This is problematic because the value of a biotechnology company to investors is based on the present value of expected future earnings of the biotechnology company. Expected future earnings of a biotechnology company equal the expected revenues derived from sales of the company's drugs if approved multiplied by the probability that the drugs will be approved. The true value of a biotechnology company equals the present value of the expected revenues derived from sales of the company's drugs if scientifically beneficial multiplied by the probability that the drugs developed will be scientifically beneficial. Therefore, the FDA's refusal to approve scientifically beneficial drugs reduces the investment value of a biotechnology company to a level below its true value. A reduction in the value of biotechnology companies reduces their attractiveness as investments resulting in less dollars being available for biotechnology companies.

C. Results: Cash Crunch for Small Biotechnology Companies

Robert T. Abbott, President and C.E.O. of Viagene, Inc. has best summarized the cash crunch faced by small biotechnology companies:

accelerated approval to those drugs which treat the groups who scream the loudest. Thus, experimental drugs for diseases such as cancer and altzheimers disease will also be given accelerated treatment as well as the AIDS drugs if a scientific review requires them to be approved.

[68] A drug is scientifically beneficial if its benefits outweigh its risks.

Most second and third tier biotechnology companies have less than 18 months of funding, many have less than 12 months, and dozens have funding for less than six months. According to a recent report by Dr. Robert Goldberg of the Gordon Public Policy Center at Brandeis University, fully *75* percent of biotechnology companies have 2 or less years of capital left. Ernst & Young reports that biotechnology companies are raising capital now at 25 percent of their burn rate (the rate at which capital is being expended.) As has already been mentioned, there are approximately 1300 U.S. biotechnology companies. That means that a staggering *975* companies will need to go to the market in the next two years or face going out of business, merging or selling rights to a larger firm. The seriousness of this situation cannot be overstated. The financing climate for biotechnology companies is, frankly, hostile. Public offerings are essentially impossible to undertake because of the depressed value of most companies' stock. This effect is indiscriminate. Virtually all companies are affected, regardless of company performance.[69]

This cash crunch in the biotechnology industry will lead to fewer biotechnology companies in the United States with a resulting decrease in biotechnology-derived drug innovation. The search for financing is driving many of the small biotechnology companies to trade precious technology for capital to foreign competitors and large domestic pharmaceutical firms.[70] Foreign competitors and

[69]Robert T. Abbott, Prepared testimony before the House Committee on Science, Space and Technology (Sept. 28, 1994), *in* FEDERAL NEWS SERVICE.

[70]Sugawara, *supra* note 53 at fi. In 1990, alliances with biotechnology companies accounted

large domestic pharmaceutical companies are the recipients of small biotechnology companies' financing troubles because these larger companies are able to acquire the technology for cheep. In addition, the failure to raise cash may cause a biotechnology company to scale back or cease operations. Companies which scale back or cease operations generally abandon potentially promising research resulting in less biopharmaceutical innovation.

Several experts agree with the theory that current government regulation will lead to a decline in small biotechnology companies making the current industry unrecognizable by the year 2000. George Rathman, founder of Amgen, the nation's leading biotechnology company and now head of ICOS Corp., stated in January 1995 that the biotechnology industry is now seriously threatened by the performance of the FDA and the incredibly slow pace of approvals.[71] Several other experts agree with Rathman but vary by the degree to which they feel small biotechnology companies are threatened. Steven Burrill, general partner at biotechnology investment banker Burrill & Craves predicts that the number of biotechnology companies may drop by almost a quarter to 1000 by the year 2000.[72] John Sterling, managing editor of Genetic Engineering News has said

for 55 percent of the 304 strategic alliances formed between drug companies. Hardy *supra* note 48 at 302. The agreements between small biotechnology companies and the larger drug companies often take many forms. The large drug company may purchase a particular technology for their sole use and development. *Id* at 302-303. Sometimes, the larger company will supply capital to the small biotechnology company and the biotechnology company in turn will agree to share any profits derived from a successful product. *Id*

[71]David Baum an, *Pharmaceutical Chief Says FDA Threatens US. Leadership,* GANNETT NEWS SERVICE, Jan. 18, 1995 at 2. A sign of the troubles faced by the biotechnology industry was the collapse of D. Blech & Co., a preeminent Wall Street biotech investment firm which recently ran out of cash. Dan Goldblatt, *Time — And Money — Are Running Out in Biotech,* 7 BUSINESS DATELINE 1(1994).

[72]Ronald E. Yates, *Biotechnology Blossoms, but Rivals Gaining on US.,* CHICAGO TRIBUNE, October 4, 1992 at 1.

that biotechnology companies may drop to 750 by the year 2000.[73] An article in the September 26, 1994 issue of Business Week predicts that perhaps three quarters of United States biotechnology firms are destined to fold or merge.[74]

Robert Abbott also foresees a dramatically different biotechnology industry in the United States in the future:

The industry is now beginning to see significant layoffs ... I believe these layoffs will forever impact our industry because of the psychological damage that is occurring. Entrepreneurial companies are staffed by people in the early, energetic part of their careers because of the long working hours and dedication required. Salaried employees often work 60 to 70 hours per week without additional compensation.

They are motivated to do this because they share in the company's vision and identify with the entrepreneurial spirit of the workplace. When, and if, such a company has its first lay-off, an irreparable break in trust occurs between the company and its employees. Sadly, it is usually the survivors of the lay-off who are the most affected. From that point forward, the work ethic is never the same. I believe that the layoffs that are now occurring, because of this longest-ever hostile financing environment, will forever change the pro-

[73] Gail Dutton, *Biotech: Risky Business?,* 84 MANAGEMENT REvIEW 36 (1995).

[74] Joan O'C. Hamilton, *An Industry Crowded with Players Faces an Ugly Reckoning,* BUS. WK., Sept. 26, 1994 at 84.

ductivity of our biotech industry, dulling it from what it has been previously.[75]

V. DETRIMENTAL EFFECTS ON THE UNITED STATES

Given that the current FDA drug approval process has created a self perpetuating cycle of capitalization problems for small biotechnology companies, it is important to evaluate the effect that a decline in the number of small biotechnology companies will have on the United States. I believe that unless the FDA reduces the cost of drug approval for biotechnology companies and removes politics from its drug approval decisions, the potential decline of small biotechnology companies will result in the following adverse effects on the United States: (1) the substantial reduction in the introduction of innovative new drugs; (2) the decline of the United States as a world leader in biotechnology; and (3) the loss of an opportunity to pursue a potential economic gold mine.

A. The Substantial Reduction in the Introduction of Innovative New Drugs

1. The demise of small biotechnology companies will reduce the introduction of innovative bio

The demise of small biotechnology companies will decrease the number of innovative new drugs introduced in the United States. A substantial proportion of the novel and innovative research in the biopharmaceutical area is performed by the approximate 1300 small biotechnology companies. The increasing number of

[75] Abbott *supra* note 69.

partnerships between small biotechnology companies and large drug companies whereby the large drug companies purchase the small biotechnology companies' technology serves as evidence of the substantial role small biotechs play in novel scientific experimentation.[76] Given the substantial role small biotechs play in biotechnology research and given the importance of biotechnology in the development of new drugs, a decline in these small biotechnology companies will decrease new drug development substantially.

There are several possible explanations for why a large share of the novel research in biotechnology takes place in the small biotechnology companies. First, financial incentives exist for scientists who engage in innovative biotechnology research to either start up their own biotechnology company or perform research for a small biotechnology company. Well known and highly respected scientists probably hold a somewhat inflated sense of confidence in their ability to produce a workable product. The successful introduction of a new drug may generate hundreds of millions of dollars for a small biotech. Therefore, a large equity stake in a small biotechnology company may be more appealing to a highly skilled scientist than a salary paid by a large pharmaceutical company. However, large pharmaceutical companies provide greater assurance to their scientists that projects will not be cut off due to lack of funds. Nevertheless, this fact is mitigated somewhat because a small biotechnology company is more likely than a large pharmaceutical company to remain faithfully committed to

[76] *5ee* Sugawara, *supra* note 53 , at fi; *see also* Sandra Sugawara, *Centocor Selling S Percent of Stock to Lilly. Firm Arranges Cash Infusion After FDA Rejection of Product Tests,* THE WASHINGTON POST, July 17, 1992 at bi.

a particular research project because unlike the large pharmaceutical company who has several other products in research, the small biotech's success or failure is based on a small number of research projects.

Second, much of the current drug experimentation and innovation is based on potential cost advantages of new products over existing products. Small biotechnology companies have a greater incentive than large pharmaceutical companies to innovate based on cost advantages of new drugs over drugs already on the market because the drugs on the market are manufactured by the large pharmaceutical companies.[77] Third, large pharmaceutical companies are constrained by their shareholders who prefer a consistent return on their investments. To the extent biotechnology research is viewed as risky without the potential for consistent returns, large pharmaceutical companies will be limited in how many resources may be allocated to biotechnology research. Unlike the shareholders of large pharmaceutical companies, shareholders of biotechnology companies do not expect consistent returns on their investment. Shareholders of biotechnology companies invest with the hope that novel biotechnology experimentation will lead to large profits in the future but at the risk of large losses.

Finally, large pharmaceutical companies have limited resources to devote to biotechnology research and have limited expertise in biotechnology. Large pharmaceutical companies, unlike most of the small biotechnology com-

[77] *5ee* Richard J. Nelson, *Regulation of Investigational New Drugs. 'Giant Step for the Sick and Dying'?,* 77 GEO. L. J. 463 (1988) (which suggests that the PMA which is dominated by large pharmaceutical companies prefers the status quo over changes that reduce the costs of drug approval because reducing the costs of drug approval decreases the barriers to small biotechnology companies from competing with large pharmaceutical companies)

panies, already have drug products on the market. Therefore, a substantial amount of a large pharmaceutical company's resources must be devoted to manufacturing and marketing activities. Large pharmaceutical companies devote approximately 15 percent of their sales revenues to research and development while small biotechnology companies devote approximately 80 percent of their resources to research and development.[78]

Furthermore, pharmaceutical companies devote a limited proportion of their research and development budget to biotechnology-derived drug development. Most drugs produced by large pharmaceutical companies have historically been derived from molecular chemistry, not biology. Therefore, over time, large drug companies have developed considerable expertise in molecular chemistry rather than in molecular biology. Any biotechnology experimentation by large pharmaceutical companies

entails shifting resources away from this area of expertise to molecular biology. In a large corporation, such a shift is undoubtedly slow and met with considerable protest.

2. The results of a reduction in innovative drug production on the United Slaks. A reduction in U.S. drug innovation will lead to two results. First, less

[78]Dutton *supra* note 73.

innovation will lead to continuing increases in health care costs. Biopharmaceutical experimentation is based on creating products with some form of a cost advantage. Biotechnology companies are working on developing cures and treatments for diseases which ultimately will reduce the cost of health care. By attacking life-threatening diseases, new biotechnology drugs will reduce the average stay in hospitals, cut the need for operations and decrease the frequency of the usage of many medicines.

Several commentators, including the Clinton administration, have argued that drug companies contribute to the rise in health care costs because of high drug prices. However, this argument fails as applied to small biotechnology companies for several reasons. First, large drug companies factor into their drug prices expenses other than research and development such as marketing costs. Since small biotechnology companies devote almost all of their resources to research and development, the prices for drugs introduced by these small biotechs will better reflect the actual cost of developing the drug. Second, the escalation in drug prices has slowed substantially. After rising at nearly double-digit rates in 1990 and 1991, average drug prices rose 5.7 percent in 1992 and 3.4 percent in 1993.[79] Third, drug prices simply reflect the cost of developing a new drug. Therefore, the FDA is partly to blame for high drug prices and a reduction in the cost of drug approval will lead to a decline in drug prices.[80] Finally, new

[79]Laurie Lewis, *Manufacturers are Under Continuing Pressure to Reduce Prices, to Improve Profitability,* 12 BUSINESS & HEALTH 23 (1994).

[80]This statement is supported by Representative Duncan from Tennessee:

Mr. Speaker, when people wonder why drugs cost so much in this country, all they need to do is look at the FDA. The over regulation and bureaucratic mumbo jumbo has helped

drugs will be marketed successfully only if they cost less than existing therapies. For example, if surgery is less costly than a new drug treatment, surgery will be preferred and the new drug will not sell.

Reduced innovation also will lead to many Americans being denied biotechnology-derived drugs which could have been developed to prevent, cure or treat their ailments. The costly FDA drug approval process inhibits advancements against diseases and prolongs victims' suffering. Many commentators criticize the FDA's drug approval process as creating a drug lag in the United States.[81] Patients in the United States receive approved drugs later than their foreign counterparts. The decline in biotechnology companies due to the FDA drug approval process leads to an even more serious result: large numbers of innovative biotechnology-derived drug therapies that would have been developed under a less stringent regulatory regime may never be developed. For example, if penicillin had not been discovered and a small biotechnology company with financing troubles was developing penicillin today, a strong possibility exists that penicillin would never be developed. The loss of even one drug like penicillin would harm more people than all of the drug toxicity in the history of modern drug development.[82]

the big drug giants, but has made it almost impossible for small companies to participate and has driven drug and medicine prices sky high. 140 CONG. REC. H6437-Ol.

[81] Several studies have been performed analyzing the effect the FDA drug approval process has oninnovation. A 1973 study by Sam Peltzman, an Economist from the University of Chicago Graduate School of Business, examined new drug innovation. He found that the United States had seen a 50percent drop in the number of drugs that reach market each year following the passage of the Drug Amendments of 1962. Peter Brimelow and Leslie Spencer, *Food and Drugs and Politics,* FORBES, Nov. 22, 1993 at 115. A recent study conducted by Tufts University found that 80 percent of the drugs approved by the FDA between 1987 and 1989 were available in other countries by an average of 6 years earlier. *Id*

[82] *5ee* John Patrick Dillman, *PrescrIption Drug Approval and Terminal Diseases. Desperate Times Require Desperate Measures,* 44 VAND. L. REv. 925, 928 (1991). For example, a 1967 to 1976delay in the approval of beta blocker compounds that treat hypertension and

B. The Decline of the United States as a World Leader in Biotechnology

Since the advent of the biotechnology revolution in the 1980's, U.S. biotechnology companies have continued to hold their worldwide lead in biotechnology innovation.[83] For example, as of September 20, 1993, figures from the United States Patent and Trademark Office show that the United States was the country of origin for 1441 of the 2094 biotechnology health care patents issued in the United States, representing almost 69% of the total.[84] Japanese companies were issued the second largest number of such patents with 13% of the total, followed by Europe with 12%.[85] However, given the increasing cost of the FDA drug approval process and the increasing reluctance of United States investors to finance such costs, as evidenced by the depressed biotech equity markets, combined with increasing foreign commitments to biotechnology, it is likely that the United States will lose its status as the world's dominant producer of biotechnology.

First, U.S. companies are being driven from the U.S. by the FDA drug approval process to places such as Europe because it is easier to conduct research

other cardiovascular diseases was responsible for over 10,000 deaths annually. *Id*

Another example of the costs of a drug not reaching the public is that of the neurological drug sodium valproate which could have prevented an estimated 1,000,000 epileptic seizures per year at a savings of $100 million in reduced disability and increased eaming capacity. *Id*

[83] Yates, *supra* note 72 at B 1.

[84] Kevin Hamilton, *PMA Finds 143 Biotech Medicines in Testing, a Gain of 80% in S Years,* BIOTECHNOLOGY NEWSWEEK 3, Sept. 20, 1993.

[85] *1d*

and development in Europe.[86] European clearance processes are quicker and easier.[87] Also, European marketing restrictions are more relaxed. Approval for a clinical trial in Europe takes about a month, while in the United States it can take up to 14 months.[88] During the ten year period from 1977 to 1987, 114 new drugs were available sooner in Great Britain than in the United States. During this same period of time, 41 new drugs were available sooner in the United States.[89] Respiratory medicines took an average of 3 years longer to be marketed in the United States and cardiovascular medicines were delayed an average of *5* years.[90] Furthermore, the gap is likely to grow with the establishment of the pan-European Medicines Evaluation Agency in l995.[91]

A vaccine which prevents Hepatitis A serves as an example of the difference between the United States' drug regulatory system and that of foreign countries. An application for the vaccine which prevents Hepatitis A was filed with the FDA in July, 1992.[92] The FDA has not approved the drug even though it was recommended for approval in 1994 by an FDA advisory committee.[93] This Hepatitis A vaccine has been approved in 40 other countries.[94]

[86]Daniel Green, *Survey of Venture and Development Capital,* THE FINANCIAL TIMES LIMITED, September 23, 1994 at IV. Capital outflow from the United States medical technology industry has increased from $321 million in 1990 to $993 million in 1994. Alan M. Slobodin and Roman P. Storzer, *FDA Paralysis Raises Health Care Costs,* 9 LEGAL BACKGROIJNDER 39 (1994).

[87]Slobodin and Storzer, *FDA Paralysis Raises Health Care Costs,* 9 LEGAL BACKGROUNDER 39 (1994).

[88]Green *supra* note 86.

[89]Slobadin and Storzer *supra* note 87.

[90]*Id*

[91]Green *supra* note 86.

[92]*Extreme Measures Against Agency Unlikely Despite Recent Criticisms,* HEALTH CARE POLICY REPORT, Jan. 23, 1995.

[93]*Id*

[94]*Id*

The creation of plants in foreign countries will inevitably lead to increasing expertise of foreign scientists in biotechnology. Also, the shifting of research and testing oversees reduces the probability that beneficial drugs will be marketed in the United States. Biotechnology companies that get a drug approved for overseas markets may not wish to invest the resources necessary to get the drug approved in the United States.

Second, foreign countries have recognized the great importance of biotechnology as a profitable business in the global economy. In 1992, Steven Burrill, then national director of manufacturing and high technology services for Ernst & Young, reported that even though American firms dominate biotechnology, Japan, France and Great Britain are equal to the U.S. industry when it comes to research.[95] Furthermore, Japan has made it a national priority to dominate the biotechnology industry by the year 2000.[96] In addition to developed countries, growing competition may also come from countries in Eastern Europe and Latin America making the transition to free-market economies.[97] These third world countries see biotechnology as an opportunity to develop native scientific talent and agricultural resources.[98]

Third, since biotechnology companies can no longer depend on the stock

[95] Yates, *supra* note 72 at 1.
[96] *Id*
[97] *Id*
[98] *Id*

market for capital because U.S. investors are reluctant to pay the excessive FDA drug approval costs for risky products, U.S. biotechs are reaching to European and Japanese investors.[99] Foreign acquisition of small U.S. biotechnology companies paves the way for Japanese and European countries to grab a stake in the global biotechnology industry. In return for the capital supplied, these foreign investors usually acquire rights in the company's valuable technology, significant equity positions in the company, and/or seats on the board of directors.[100] Due to small biotechnology companies' need for capital, foreign companies are able to extract substantial value from the small biotechnology companies in return for the capital supplied.

Foreign acquisitions of U.S. biotechnology companies during the 1990's have included: Japan's Chugai Pharmaceuticals Inc's acquisition of Gen-Probe, Inc; Germany's Schering AG's acquisition of Triton Biosciences Inc.; France's Sanofi's acquisition of Genetic Systems Corp.; and Switzerland's Roche Holding Ltd.'s acquisition of a sixty percent share in Genentech, Inc.[101] These acquisitions along with the multitude of other foreign acquisitions of small U.S. biotechs raises concerns about the selling of U.S. technology to foreign companies. Generally, these mergers create a flow of information out of the United States into foreign countries without a corresponding influx of technology into the United States.[102] This outflow of information strengthens the foreign markets and

[99] *5ee* Sugawara, *supra* note 53.
[100] *5ee* Yates *supra* note 72; *see also* Sugawara, *supra* note 53.
[101] Hardy *supra* note 47.
[102] *Id.*

weakens the United States' ability to compete and commercialize this technology.[103]

The decline of the United States' dominance in the biotechnology industry is problematic for two reasons. First, increasing competition in the global marketplace in biotechnology increases the competition for financing. This increase in competition perpetuates the current problems for small U.S. biotechnology companies – the lack of money to finance drug approval.

Second, biotechnology like computer chip technology, communication technology, etc. may be a source for considerable future revenues derived from both sales in the United States and abroad. Thus, if the U.S. biotechnology industry remains dominant in the global market, the U.S. will generate a substantial trade surplus in biotechnology-derived drugs. As an example, innovation fostered by successful investment has produced a *$5* billion trade surplus in 1993 on exports of $15 billion in the medical device industry.[104] A trade surplus in the biopharmaceutical drug industry will reduce the United States deficit while a trade deficit in this industry will lead to the opposite result. Therefore, prosperity in the biotechnology industry has far reaching budgetary consequences. Consequently, the U.S. should take rational steps to prevent the erosion of its global dominance of the biotechnology industry.

C. **The** Loss **of a Valuable Economic Opportunity**

[103] *Id.*
[104] Slobodin and Storzer *supra* note 87.

A 1994 Ernst & Young survey of the biotechnology industry found that there are 1272 biotechnology companies in the United States.[105] These 1272 biotechnology companies employ approximately 100,000 highly skilled, highly paid people nationwide.[106] Current annual industry revenues total approximately $11.2 billion.[107] Given the infancy of the biotechnology industry and its importance to future drug development, the industry has the potential to grow at an extremely fast rate with an accompanying growth rate in skilled jobs. These 1272 small biotechnology companies have the potential to earn $100 billion by the year 2000.[108] Sales of biopharmaceutical drugs alone have the potential to reach $60 billion by the turn of the century. [109]

Several areas in this country depend on the biotechnology industry for the jobs it produces and the income it generates. For example, California is the home of 30% of U.S. biotech companies and provides 38% of the biotechnology industries' jobs.[110] Given the importance of biotechnology in California, it is understandable why the Los Angeles Times in 1993 stated that growth in the biotechnology industry is essential to California because growth in the biotechnology industry counteracts the fear that the state's prolonged recession will tilt the job base away from skilled jobs, represented by declining industries such as

[105] Eckhouse, *supra* note 48 at Bi.
[106] *Id*
[107] *Biotech Down, But Don 't Count it Out, Analyst Says,* THE SUNDAY GAZETTE MAIL, Nov. 20, 1994 at lOB.
[108] Hardy *supra* note 47.
[109] *Id.*
[110] *Id.*

aerospace, toward low-wage manufacturing and service jobs.[111] The Los Angeles Times also reported that the key to biotechnology's expansion in California is that venture capital continues to pour in.[112]

Baltimore, Maryland, Cambridge-Boston, Massachusetts and New Jersey also possess substantial economic interests in the survival of the biotechnology industry. Baltimore has spent substantial sums to attract biotechnology companies to the Baltimore area. Baltimore believes that the biotechnology industry can revitalize its downtown area which was left with little financial resources after young professionals moved out of downtown.[113] The Cambridge-Boston area also has a substantial economic stake in the biotechnology industry. Within this area is one of the largest congregations of biotechnology companies in the country.[114] New Jersey is the fourth largest center of biotechnology companies in the U.S. There are an estimated 80 biotechnology companies in the state.[115]

Given biotechnology's current and potential economic importance, the U.S. economy will suffer from a decline in the biotechnology industry. For example, ImmunoGen, Inc.'s troubles cost the Cambridge-Boston area over 100 jobs and accompanying economic problems. ImmunoGen Inc. laid off 102 employ-

[111] Chris Kraul, *Biotech Blossoms: Industry Hiring is Up Despite Statewide Slump,* L.A. TIMES, July28, 1993 atBi.

[112] *Id.*

[113] Roy Furchgott, *Baltimore has Seen the Future, and It is Biotechnology,* N.Y. TIMES, August 28, 1994 at Section 3, page 7; *See also* Lori Silver, *Biotech 's Stunted Growth; NIH Influence, Lack of Capital Slow Maryland Firms in Race to Develop Drugs,* THE WASHINGTON POST, October 8, 1990 at 1.

[114] Ronald Rosenberg, *Biotech Gold Lures New Wave of Cash,* BOSTON GLOBE, November 12, 1991 at 37.

[115] 19 of these 80 biotechnology companies are publicly held. *Id*

ees and temporarily closed two manufacturing facilities after learning that an expected $20 million investment from a European pharmaceutical company fell through.[116] ImmunoGen Inc. is illustrative of the problems faced by most small biotechnology companies today. ImmunoGen Inc. has a product in phase III of the FDA approval process. ImmunoGen had raised $130 million, but is now left with only $11 million in cash.[117] Therefore, cutting costs was ImmunoGen's only alternative.[118]

VI. ANALYSIS OF PROPOSED REFORMS

A multitude of proposed reforms have arisen out of the criticism directed at the FDA drug approval process. The preponderance of the proposals generally fit within one of two classes: (1) Re-structuring or replacing the FDA to ensure more efficient review of new drug applications and more scientifically-based standard setting; and

(2) De-regulation of the drug approval process so that drugs reach the market sooner. I will analyze some of the current proposal's effects on small biotechnology companies and on the welfare of the United States. I will then present my own proposals which I feel will benefit biotechnology companies without imposing unnecessary risks on the U.S. population.

A. The Players

[116] Ronald Rosenberg, *ImmunoGen Lays off 102, Shuts 2 Plants,* BOSTON GLOBE, December 20, 1994 at 41.
[117] *Id.*
[118] *Id.*

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Reforming the FDA drug approval process to reduce the cost of drug approval has gained the attention of a new coalition of industry critics, conservative groups and powerful Republican lawmakers.

1. The Progress & Freedom Foundation. The Progress & Freedom Foundation, a think tank affiliated with House Speaker Newt Gingrich, has raised $400,000 from drug, biotechnology and medical device companies in part to finance a study on how to reform the FDA and its drug approval process.[119]

2. Citizens for a Sound Economy. Citizens for a Sound Economy, a conservative advocacy group that has made public an opinion survey critical of the FDA by an influential pollster is preparing a grass routes drive to build Congressional support for revamping the FDA.[120]

3. Thomas J. Bliley. Jr. House Commerce Committee Chairman, Thomas

J. Bliley Jr., Republican from Virginia who also heads the House Biotechnology Caucus will champion Congressional hearings to be begun in 1995 which will scrutinize the FDA's operations.[121]

4. Newt Gingrich. Speaker of the House of Representatives, Newt Gingrich,

[119] Peter H. Stone, *Ganging up on the FDA,* NATIONAL JOURNAL, Feb. 18, 1995 at 410.
[120]
[121] *1d, See also* Steve Usdin, *Good vs Perfect,* BIOCENTURY, Jan. 30, 1995 at 1.

is the grandfather of the FDA reform movement. He has publicly denounced the agency as the leading job killer in America.[122] He has deemed FDA Commissioner David Kessler to be a bully and a thug.[123] In the fall of 1994, he urged a crowd of biotech executives to work with the Progress & Freedom Foundation on its study and brought a top biotech industry executive onto his cable television show to discuss major changes to the FDA.[124]

5. The Biotechnology Industry. On February 8, *1995,* about *55* biotech executives made a pilgrimage to Washington D.C. where they met with several members of Congress including Representative Joe L. Barton, Republican from Texas, the Chairman of the Commerce Oversight Subcommittee, to discuss FDA reform.[125] The industry is likely to play a prominent role as FDA reform battles heat up.[126] The reforms sought by the biotechnology industry include faster drug approvals, privatizing some of FDA's functions and eliminating inconsistencies between regulations of drugs and biologics.[127]

6. Pharmaceutical Research and Manufacturers of America (PhRI\4A). PhRMA will likely play a prominent role in FDA reform. PhRMA President Gerald Mossinghoff said that the group might suggest that the FDA privatize key missions, including NDA reviews.[128] Their goal is to get the FDA to em-

[122]John Carey, Joseph Weber and Joan O'C. Hamilton, *Is the FDA Hooked on Caution?,* BUS. WK., Jan. 30, 1995 at 74.
[123]*Id.*
[124]Stone *supra* note 119 at 410.
[125]*Id.*
[126]
[127]
[128]Usdin *supra* note 121 at3.

ulate the European system in which reviewers are drawn from industry and academe.[129] Mossinghoff has also called for a reduction in the FDA's requirements for documentation, especially for early stage clinical trials.[130]

B. Restructuring the FDA: The Issue of Privatization

Several different proposals to restructure the FDA to increase the efficiency of drug approval in the United States have been mentioned over the past year. First, I will analyze a current proposal to revamp the FDA replacing it with a private body to regulate drug approvals. Then, I will propose a modified version of this privatization proposal which I feel will better serve the biotechnology industry and the United States. Finally, I will demonstrate why less radical reforms will fail to improve substantially the current system.

1. The Proposal: Replacement of the FDA with a Private Organization Responsible for Drug

Several politically powerful individuals and organizations favor replacing the FDA with a private organization to review drug applications and to set drug approval standards.[131] This private organization would be staffed with members of the drug industry, including scientists, doctors and medical entrepreneurs.[132]

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131 *5ee* Lisa Nevans, *Republicans have Talked of Killing off the FDA: Agency Faces Uncertain Future,* THE WASHINGTON TIMES, Dec. 27, 1994 at CS (for example Newt Gingrich in September launched a Medical Innovation Project to design a replacement for the FDA while other conservative think tanks are working on proposals to privatize the entire drug approval process and/or dismantle the FDA).

132 1f conflicts of interest arise in the review of a new drug one of two things may be done: (1) the reviewer with a conflict would have to disclose it and continue to review the drug which generated the conflict or (2) the reviewer with the conflict would have to withdraw

According to the proposal, Congress would ordain the group with the exclusive statutory authority to review and approve new drugs.[133] This new private agency would take on all of the FDA′s current duties with regard to the approval of new drugs.[134] The agency would be responsible for setting the data requirements necessary for approval, for establishing the regulations concerning preclinical and clinical trials and for reviewing all data and making drug approval decisions based on that data.

2. Justifications for proposal. The influence of political pressure on the FDA stands as the primary justification behind this proposal to revamp the FDA and replace it with an independent private agency. Since the FDA has been unable to regulate drugs based solely on scientific merit, replacing the FDA with a private independent organization removed from the influence of Congress frees the review process from political conservatism.

Lawmakers have several means to ensure that the newly formed private organization remains outside of the political pressures of Washington. First, Congressional involvement with the new agency must be limited. Therefore, Congress′ role would be limited to granting statutory authority to the new organization and to funding the organization[135]. Second, drug reviewers must be subject to strict term limits. Term limits would ensure that the organization

from reviewing the drug.

[133]

[134]

[135]Congress should defer to the expertise of the new private agency as to the amount of funding necessary to conduct an efficient review.

will be staffed by individuals who have no long term connection to the political machinery in Washington D.C.

The fact that the FDA is an inefficient governmental bureaucracy serves as a second justification for replacing the FDA with a private organization. According to this argument, the FDA is an inefficient governmental agency which fails to promote good work and fails to punish abuses of discretion. FDA employees like employees of other governmental departments are accused of not having the correct incentives to efficiently analyze data. Representative Duncan from Tennessee has made this argument against the FDA on the floor of the House of Representatives:

Mr. Speaker, when people wonder why drugs cost so much in this country, all they need to do is look at the FDA. The over regulation and bureaucratic mumbo jumbo has helped the big drug giants, but has made it almost impossible for small companies to participate and has driven drug and medicine prices sky high.. . Why, Mr. Speaker, is there all this waste and inefficiency, all this arrogance and abuse of power? I believe it is primarily because of our civil service system, a system that does almost nothing for good, dedicated employees, but serves now to protect lazy and incompetent ones. We have many good people working for our Federal Government, but we cannot get rid of those who don't work hard or those who treat people badly.[136]

[136] 140 Cong. Rec. H6437-01, July 28, 1994.

3. Benefits of the proposal. Replacing the FDA with a private reviewing body will benefit small biotechnology companies in three ways: (1) Drug review times will decrease; (2) The likelihood of approval will increase; and (3) Data requirements and pre-clinical and clinical regulations will decrease.

a. Decreased drug review times. Drug review times will decrease dramatically. Political conservatism on the part of the FDA has slowed the review of drugs substantially. The influence of politics on the FDA has manifested in FDA demands for more data, in FDA requirements of longer periods of testing and in FDA's extensive scrutiny of data beyond what is scientifically necessary. Decision making based solely on science will reduce the delays caused by political conservatism. In addition, more efficient review of drugs will reduce review times.

Lengthy review times of completed NDAs hurt small biotechnology companies. Currently, a biotechnology company must wait approximately 20 months after the completion of Phase III clinical tests for an approval/non-approval decision to be made by the FDA.[137] The FDA estimates that companies may earn an average of $10 million for each additional month they have a drug on the market.[138] In other words, biotechnology companies lose approximately $10 million

[137]Piercy *supra* note 33.

[138]Sandra H. Cuttler, *The Food and Drug Administration's Regulation of Genetically Engineered Human Drugs,* 1 J. PHARMACY AND LAW 191, 208 (1993).

for each month that approval is not granted following completion of clinical testing. Such a loss of money diminishes the return to investors in biotechnology companies that successfully develop a drug product. Lower returns from developing drugs translate into lower investor valuations of biotechnology companies which contributes to the drying up of the biotech equity markets.

Shortening the NDA review process is critical to the improvement of the biotechnology industry. For example, cutting the NDA review time by 15 months (from the current 20 months to 5 months) would enable biotechnology companies to generate approximately $150 million during a period of time in which these biotechs currently receive no revenues. Expectations of greater revenues due to faster approval times increases the expected rate of return of biotechnology companies encouraging investment in biotechs alleviating the cash crunch faced by the industry. Furthermore, decreasing the length of time that a small biotechnology company must finance all operations through outside sources rather than through revenues generated from sales of a new drug decreases the risk that the company will cease operations due to a lack of capital.

b. Greater probability of approval. Private review of drugs will lead to a higher probability that an NDA will be approved than under the current FDA regime. Since FDA$'$s failure to approve drugs is often the result of political conservatism rather than of scientific decision making, a private review organization, which is removed from politics, will approve more drugs. For example,

Varivax, the chicken pox vaccine, was approved by two private advisory committees.[139] Yet, the FDA refused to approve the drug for several years.

An increased probability of drug approval increases the value of biotechnology companies to investors and reduces the cash crunch problem. As stated earlier, the value of a biotechnology company to investors is based on the present value of expected future earnings of the biotechnology company. Expected future earnings of a biotechnology company equal the expected profit derived from sales of drugs currently being developed if approved multiplied by the probability that the drugs will be approved. The true value of a biotechnology company equals the present value of the expected earnings derived from the development of scientifically beneficial drugs. Currently, because the FDA refuses to approve many scientifically beneficial drugs, biotechnology companies′ investment values are less than their true values. Therefore, a private drug approval body, by basing drug approval on science alone, will elevate the investment value of biotechnology companies to their true values which will encourage greater investment in biotechnology companies.

c. Less regulation. Data requirements and pre-clinical and clinical regulations will decrease. Much of the FDA′s over caution has manifested itself in substantial data requirements and pre-clinical and clinical regulations. For example, the current NDA application, which contains all of a drug′s data necessary for an approval decision, may number in the hundreds of thousands of

[139] 5ee Carey *supra* note 122.

pages.[140] Also, the FDA has come under fire for implementing excessive regulations in the early stages of clinical trials.[141] In most cases, the early regulations are simply to protect a limited number of test subjects. According to the Health Care Policy Report:

George B. Rathman, chairman and chief executive officer of ICOS Corp., a biotechnology firm, ... said a major problem is the excessive caution of FDA regulators during early clinical trial studies. He said companies that recommend a reasonable risk level are instead faced with FDA suggestions and proposals to increase dose levels, build in lengthy observation periods, and schedule discussions with the FDA at each stage.[142]

Under the plan to replace the FDA with a private organization removed from politics, it is inevitable that much of the current unnecessary regulatory regime will be discarded. One of the missions of the private organization will be to design the regulatory structure of drug review. In doing so, the private organization will apply a cost benefit analysis to regulations. Therefore, if a regulation's costs outweighs its benefits then the regulation will be eliminated. For example, if the required 12 months of chronic toxicity tests in two species of animals during pre-clinical studies is extremely costly but produces little benefit in protecting Phase I test subjects, it will be reduced or eliminated altogether.

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[142] *Extreme Measures Against Agency Unlikely Despite Recent Criticisms,* HEALTH CARE POLICY REPORT, Jan. 23, 1995.

A reduction in the data requirements for drug approval benefits small biotechnology companies. A reduction in data requirements and regulations reduces the cost of drug approval. Therefore, small biotechnology companies will require less capital to sponsor a drug. This will enable these small biotechnology companies to diversify their portfolio of drugs which will reduce the risk of investing in small biotechnology companies. Reducing the risk of biotechnology companies will increase their expected returns. As a result, the industry′s capital crunch will be alleviated substantially.

4. Disadvantages to this proposal. Even though the proposal to completely remove FDA from the drug approval business and replace it with a private organization has considerable merit, there are several reasons why such a dramatic measure should not be undertaken.

a. Fraud and corruption. Handing responsibility for drug approval over to the drug industry subjects the drug approval system to a substantial risk of fraud and corruption. A primary concern is that members of a private review organization will be more likely to accept bribes than members of the FDA. Currently, Congress′ wide ranging ability to discipline the FDA is sufficient to prevent industry corruption of the FDA.[143] However, a private review organization would remain outside of Congress′ control, and therefore regulating

[143] *5ee* Beckner *supra* note 57.

industry corruption of the private review organization would be extremely difficult. Attempts by the industry to bribe the FDA have been common in the past. For example, in 1989 revelations of corruption among FDA employees and the generic drug industry came to light.[144] Generic companies made illegal bribes to FDA employees and phony bioequivalence testings comparing the new drug to itself were used to gain approval.[145] In response to increased Congressional oversight of the FDA following the generic drug scandal, the FDA instituted several important internal reforms which reduced the likelihood of future corruption.[146]

Another argument may be asserted that a private review organization may be biased toward the approval of new drugs because of their ties to the drug industry. In other words, a private review organization may take a completely opposite approach to drug approval than the FDA endangering public health. While the argument that a private review organization may be subject to more corruption than FDA has considerable merit, I do not believe that such a private review organization will hold a bias toward approval of drugs which have questionable scientific merit. First of all, conflicts of interests can be eliminated. Second, scientists and doctors are likely to base their decisions solely on scientific merits to preserve their scientific reputations. Third, the interests of different members of the drug industry often do not coincide. For example, a large phar-

[144]Bruce Kuhlik, *The Origins of the Generic Drug Scandal and Proposed Amendments to the Federal Food, Drug and Cosmetic Act,* 45 Food Drug Cosm. L. J. 385, 390.

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maceutical company may be better off by a slow, costly drug approval process because such a process serves as a barrier to entry for small biotechnology companies who wish to develop products to compete with the large pharmaceutical company.

b. The appearance of Impropriety. The lack of a governmental organization responsible for drug approval creates the appearance of impropriety concerning drug approvals creating a loss of faith in the safety of the drug supply. Currently, the stamp FDA Approved upon a drug generates confidence in the market that the drug is safe and effective. As a result, individuals are willing to use the FDA approved drug in order to cure or treat their ailment. Therefore, drug companies, including biotechnology companies, are assured that their product will have a market upon approval and approval will result in considerable profits. On the other hand, a stamp on a drug stating Industry Approved fails to convey to the public the same level of confidence in the safety and effectiveness of the particular drug. A general public perception exists, whether accurate or not, that the drug industry′s interests do not coincide with the public′s interests. Thus, the public may equate such an approval with an advertisement rather than as a certification of a drug′s safety and effectiveness.

Since the demand for drugs is based on consumers confidence in the safety and effectiveness of the drug supply, if public confidence declines, demand for drugs will decline. As a result, drug sales will decline and the industry will lose profits. Therefore, eliminating the FDA entirely from the drug approval business and replacing it with a private organization may actually hurt

biotechnology companies. A decrease in expected profits may completely offset any gains from decreased costs associated with a private review of drugs.

c. Loss of FDA expertise. An argument may be asserted that taking the FDA out of regulating drug approval would be foolish because the FDA has developed considerable expertise after 30 years of experience with reviewing drugs. However, during these 30 years the FDA has added regulation after regulation based on its political conservatism increasing the cost and time necessary for approval of a drug. Therefore, replacing the FDA with a private review organization is justified simply because it will undo some of the FDA′s past 30 years of work.

d. Not politically accountable. Another argument may be asserted that review of drugs, which affects the lives of approximately 250 million American citizens, should be conducted by a politically accountable organization such as the FDA rather than by a private organization. Such an argument is based on a libertarian notion that in a democracy individuals should have at least an indirect voice in policies which affect them. According to the argument, if individuals desire a greater supply of drugs rather than extra safe drugs, such a result should be the product of the political process. Even though this argument sounds compelling, I disagree with it. As I have argued earlier, the political process leads to an inefficient level of drug production resulting in beneficial drugs not being available to individuals who need them. The political process will not work in the drug approval arena because of the inefficient distribution

of information to the public. The public takes quick notice to 5 children who die in a clinical trial. However, the fact that a more efficient system would produce more drugs to treat the thousands of individuals who suffer each day from diseases often goes unnoticed.

5. A better solution: modified privatization. From the foregoing discussion, it is clear that privatizing the drug approval process holds substantial merit. However, removing the FDA entirely from the drug approval process creates problems of corruption and the appearance of impropriety. Therefore, I propose the following drug regulatory structure:

a. A private review organization (which I will call PRO for purposes of this proposal) should be established to review all drug data and make all drug approval decisions. A summary of all data concerning a drug reviewed by the PRO sufficient to enable the FDA to assess a drug′s scientific costs and benefits must be sent to the FDA.

b. The PRO will be responsible for setting and implementing all of the regulations concerning drug approval. This includes determining what data is required for the NDA, how pre-clinical and clinical trials shall be conducted, what types of steps must be taken in order to protect clinical subjects, etc.

c. The FDA will regulate the PRO in the following ways. First, the

FDA will establish conflict of interest rules and enforce these rules. Second, the FDA will establish certain PRO internal procedures necessary to minimize the risk of corruption within the PRO. Third, the FDA will be responsible for setting rules against industry fraud and corruption or against those industry practices that have a dangerous likelihood of leading to the corruption of the PRO. The FDA will also be responsible for enforcing these rules such as through the imposition of sanctions. Fourth, the FDA may also pass rules requiring informed consent of test subjects. However, these rules may not address the amount of data required prior to testing on clinical test subjects.

d. The FDA may also issue policy statements governing the approval of drugs. These policy statements will serve as advisement′s to the PRO and will not be binding upon the PRO.

e. Upon approval of a drug by the PRO the drug is deemed to be approved by the FDA 30 days following the PRO′s approval of the drug. If the FDA wishes to challenge the PRO′s approval of a drug, a suit must be instituted in Federal Court within this 30 day period. To prevent a drug from being approved, the FDA must prove with clear and convincing evidence that the drug′s scientific costs outweigh its scientific benefits. If a suit is filed, the FDA may seek a preliminary injunction against distribution of the drug for a maximum period of 60 days following PRO′s approval of the drug. This preliminary injunction may be extended until completion of the suit, if the court is convinced that distribution of the drug endangers the health and safety of

the public. Endangering the health and safety of the public does not include the harm resulting from the use of an ineffective product.

f. Congress shall maintain all of its current avenues of direct control over the FDA. Congress′ direct control over the PRO shall be limited to funding. This proposal ensures all the benefits of privatization, while eliminating most of the costs. This proposal overcomes the twin evils addressed by the Privatization Proposal – conservative politics and governmental inefficiencies – by placing drug approval in the hands of the PRO. Congress is one step removed from influencing the PRO and therefore the PRO will be insulated from Washington politics. Congress maintains the ability to influence the FDA. However, my proposal limits the ability of the FDA to influence the PRO. FDA is not allowed to regulate the scientific method conducted by the PRO. Rather, FDA′s role is to ensure that the PRO′s process of reviewing data and setting standards is not influenced by industry corruption. The FDA may challenge the PRO′s approval of a given drug, yet a hefty clear and convincing evidentiary standard must be met. Therefore, the only drug approvals that will be overturned will be ones approved under the specter of fraud or gross negligence.

In addition, my proposal eliminates the two disadvantages of the Privatization Proposal – risks of corruption and appearances of impropriety. Under my proposal, the FDA is given considerable latitude to prevent and punish PRO corruption. Following the generic drug scandal in 1989, FDA passed several internal procedures strengthening the FDA to eliminate the risk of corruption

within the FDA.[147] Likewise, I believe that the FDA will be able to regulate the PRO to prevent corruption. Second, since the new system implements FDA oversight over the PRO, greater confidence will be generated in the market concerning the effectiveness and safety of the drug supply. In addition to the FDA′s ability to prevent PRO corruption, all drugs approved by the PRO will be stamped FDA Approved. The FDA will receive summary information concerning each drug reviewed by the PRO and will have the opportunity to challenge any drug that is approved by the PRO. The regulatory framework I propose maintains the FDA as ultimately responsible for the safety and effectiveness of the drug supply. Therefore, demand for drugs will remain strong because the market will remain confident in the safety and effectiveness of new drugs.

6. Other proposed solutions to restructure the FDA will fail to produce an efficient outcome.

Countless numbers of other proposals to re-structure the FDA in order to improve the efficiency of the drug approval process have been offered. For example, Dr. Sidney Wolfe has argued that rather than tearing down the FDA we should strengthen it by supplying the FDA with more money.[148] Other proposals have been made to require the FDA to make greater use of advisory groups to review drug data and to make approval decisions.[149] While both of these proposals address some of the current problems with the FDA drug approval process, both fall short of promoting both the efficient development of scientifically beneficial

[147] 5ee Kuhlik *supra* note 144.
[148] Sidney W. Wolfe, M.D., Prepared Testimony before the House Committee on Appropriations, Subcommittee on Agriculture, Rural Development and Related Agencies Hearing on FDA Appropriations (Jan. 31, 1995) *in* FEDERAL NEWS SERVICE.
[149] *5ee* Stone *supra* note 119.

drugs and the efficient approval of scientifically beneficial drugs.

a. Expanded FDA. Supporters of expanding the FDA argue that greater financial resources will lead to faster drug approvals.[150] These supporters believe that the true problem with the current drug approval process is the 20 months it currently takes to review an NDA.[151] Greater financial resources will lead to more FDA personnel and a higher level of scientific expertise in the agency. More personnel and greater scientific expertise should reduce backlogs and increase efficiency. Consequently, review times should decrease.

Evidence exists to support this theory. Since the passage of the User Fee Act of 1992, drug review times have steadily decreased. For example, the average time it took for the FDA to approve a new drug in 1994 was 19.7 months down from the 26.5 months in 1993 (a 26% reduction).[152] Furthermore, Kessler has stated that the FDA plans to reduce review times to less than a year by *1997.*[153]

[150]Two viable sources for increased funding exist: (1) tax revenues and (2) fees from drug companies. If increasing the funding of FDA reduces the length of time of approvals, an argument can be made that the government is justified in tapping either of these sources. If the length of time for approvals decreases, more drugs will be developed and health care costs will decrease. Therefore, taxpayers should be willing to bare the burden of an increase in taxes to support the FDA because they will be compensated by lower health care costs. Second, user fees could be adjusted to finance FDA′s decrease in drug approval time. On October 29, 1992, the President signed into law the Prescription Drug User Fee Act of 1992 which granted the FDA the right to collect more than$325 million over 5 years in user fees from research-based pharmaceutical companies. User fees could simply be raised to finance the increase in FDA personnel. Furthermore, to help smallbiotechnology companies, the user fee might only be raised for those drug companies who already have drugs on the market. For example, the user fee for each product on the market may have to be increased from $6000 per year to $25,000 per year while application fees for new products will not be raised. Thus, the increase in user fees will result in an indirect transfer of wealth from established drug companies to the small biotechnology companies.

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[152]Piercey *supra* note 33 at 1.

[153]Carey *supra* note 122 at 73.

However, increasing the financial resources of the FDA fails to eliminate political conservatism from drug approval. Greater financial resources do not counteract the fact that the FDA outright refuses to approve certain scientifically beneficial drugs. Nor does this proposal in any way alleviate the problem of excessive regulations in the pre-clinicals and clinicals. According to George Rathman, Chairman and CEO of ICOS Corp. one of the major roadblocks to biotechnology drugs is:

over-regulation and over-caution during Phase I and Phase II trials. People are focusing on review times at the FDA when the real bottleneck is the first five or six years of clinical investigation. .. User fees address the problem late in the game, in the last year and a half of the drug development process.[154] Furthermore, this proposal inadequately addresses the problem of FDA inefficiency. Increasing the number of personnel will decrease the time required for approval. However, increasing personnel will not remove the FDA′s inability to create ideal incentives for its employees to review data efficiently. As a result, much of the increases in financing will be wasted as is current funding of FDA.

b. Greater use of advisory groups. Moderate versions of the privatization proposal have arisen. For example, several groups have argued that the FDA should make greater use of private advisory groups to review data and make drug approval decisions with the FDA having final say over any drug approval.[155] The targeted benefits from such a system are the same as pri-

[154]Piercy *supra* note 33 at 5.
[155]*5ee* Stone *supra* note 119; *See also* Usdin *supra* note 121.

vatizing. The use of private advisory groups introduces a politically unbiased scientific decision maker into the drug approval process who will approve drugs on scientific merit alone.

However, this proposal will not result in an efficient level of drug development and approval for two reasons. First, if the FDA has a veto power over these advisory groups, the advisory groups are rendered virtually useless. For example, earlier in this paper, I mentioned the failure of the FDA to approve Varivax, a chicken pox vaccine. Two advisory groups recommended approval of that drug and yet the FDA refused to act on these recommendations. Therefore, this proposal will not produce an efficient level of drug approval. Second, even if the FDA follows the advisory group′s approval recommendation every time, the reform still fails to get rid of the FDA′s over regulation of pre-clinicals and clinicals which reduces the level of drug development. Thus, this proposal fails to achieve the efficient level of drug development. The best solution is to hand over standard setting functions for drug testing to a private group.

B. Deregulation of the Drug Approval Process

Numerous proposals to deregulate the drug approval process reducing the cost of drug approval have arisen during the past year. These proposals differ from privatization proposals by addressing the manner in which the FDA regulates drug approval rather than by focusing on which entity regulates drug approval. In analyzing the deregulation debate, I will keep this debate separate

from the privatization debate. I will not address the effects of privatizing the FDA on the deregulation debate. However, since I believe that my privatization proposal will lead to the efficient level of regulation, if my privatization proposal is accepted, a debate over deregulation in unnecessary. Therefore, my analysis of the deregulation debate will assume that the FDA maintains control over the drug approval process. First, I will focus my analysis on a current proposal to eliminate all requirements of FDA approval for a drug to be marketed. Then, I will propose other deregulatory reforms which will better serve the interests of small biotechnology companies and the United States.

1. The Proposal: Elimination of the requirement of pre-market approval. Several commentators have argued for the most radical form of deregulation of the drug approval process: elimination of the requirement of pre-market FDA approval of a drug.[156] For example, the Washington D.C. based Competitive Enterprise Institute proposes that the FDA should be stripped of its veto power over the approval of drugs.[157] The Competitive Enterprise Institute argues that the FDA should serve as a certifying agency.[158] If a drug is demonstrated to be safe and effective in treating X disease according to the stringent FDA standards, the drug would be certified as ˜FDA approved for the treatment of X disease. If the drug does not meet the FDA standards, the drug will be stamped with The FDA has not approved this drug to be safe or effective in

[156] *5ee* Usdin *supra* note 121. *See also* Peter Brimelow and Leslie Spencer, *Food and Drugs and Politics,* FORBES, Nov. 22, 1993 at 115.

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the treatment of any disease. The Competitive Enterprise Institute feels this modified regulation combined with common law negligence will serve the twin interests of protecting the public while encouraging the efficient level of new drug development.[159]

Other commentators have supported a modified form of this proposal. These individuals have asserted that the FDA should only require proof of a drug's safety prior to approval. For example, Frederick Beckner, in an article written in the Georgetown Law Journal, argues that the current drug review procedures should be modified so that once a drug's safety is established, the FDA should allow it to be marketed.[160] He argues that the drug manufacturer should not be required to undertake the costly phase III clinical trials to demonstrate the drug's effectiveness.[161] Rather, Beckner believes that information disclosure should take the place of FDA approval in allowing consumers and physicians to make informed choices about what drugs to take[162] 2. Benefits from proposal. The benefits from eliminating pre-market approval are obvious. Eliminating the current regulatory requirement for drug approval will substantially increase drug innovation benefiting both the drug industry and individuals in need of

[159] Brimelow *supra* note 156.

[160] Beckner *supra* note 57 at 559-561.

[161]

[162] *Id.* Beckner believes that standardized scores provide an effective way to convey drug information to consumers. By referring to a scoring system, consumers will be able to make comparisons between products. Without such a scoring system, no such comparisons will be able to be made. According to his argument, a single standardized system allows information to be conveyed to consumers and physicians cheaply and efficiently. Under his scoring system, the manufacturers will have to disclose the amount of time a drug has been tested, the observed sideeffects of the drug, and the severity of the side effects in a systematic, standardized manner. Furthermore, manufacturers would be allowed to supplement this required information with additional information.

innovative therapies.

a. Benefits to small biotechnology companies. Eliminating the requirement of FDA approval creates obvious benefits for the biotechnology industry. This proposal eliminates the FDA approval process as the primary barrier to a drug reaching the market. The *$350* million that currently must be invested before a drug may be marketed will be substantially reduced by this proposal. No other proposal goes further to eliminate the cash crunch in the biotechnology industry.

b. Benefits to patients. This proposal will benefit patients in need of innovative treatments. With no barrier to selling drugs to sick individuals, drug development will increase substantially. Currently, a multitude of potential drugs are not being developed because of the exorbitant cost of FDA drug approval requirements. Therefore, drug production and innovation will increase substantially with the passage of this proposal. Patients with life threatening diseases will gain access to a much broader array of products with potentially beneficial affects. Furthermore, other individuals who have ailments which are not life threatening and therefore have not been allowed quick access to experimental drugs under current regulations also will gain access to a much larger selection of drugs.

Also, patients will benefit from lower health care costs. This proposal will drive down drug prices and the cost of health care. Drug companies will no longer have to charge high drug prices to recapture their drug approval costs. Also, competition between a wide array of new drugs will drive the prices

down. Lower drug prices combined with a wider array of drugs will lead to lower health care costs. 3. Costs outweigh benefits of proposal.

a. Problem of Asymmetric Information: Results in too much demand for drug products. If drug consumers held perfect, costless information of the benefits and side effects of all drugs on the market, the proposal to remove pre-market approval would be an ideal solution to alleviate problems suffered by the biotechnology industry. Consumers could decide whether to take a drug or not based on their own cost benefit analysis. Even if consumers did not hold perfect information this proposal would lead to an ideal result if their doctors held perfect information and they acted solely in their patient's interest.

Unfortunately, neither consumers nor doctors have perfect information. Manufacturers lack sufficient incentives to provide full information about their drug products and this information is otherwise unavailable or too complex to evaluate.[163] Manufacturers lack the incentives to produce drug information for two reasons. First, customers are generally unsophisticated and even if they are given all the information, they will be unable to make an accurate cost benefit analysis without the advice of a doctor. Second, an agency problem exists between doctors and their patients.[164] Doctors, who are generally responsible for making the cost benefit analysis for a patient, do not bear the costs of the drug's side effects.[165] Therefore, doctors do not have the correct incentives to

[163] *1d See also* Henry Beales et al., *The Efficient Regulation of Consumer Information,* 24 J.L. & ECON. 491 (1981).

[164] *5ee* Beckner *supra* note 57.

[165] While a patient may sue a doctor for medical malpractice, it is unlikely that this threat will cause doctors to acquire all information conceming a drug's costs and benefits because it is doubtful that a doctor would be found liable for malpractice for not evaluating all of the available data on a given

evaluate all information on a drug′s costs and benefits.

Even if drug companies provide information on drug products, experience has proven such a distribution of information fails to adequately instruct doctors or their drug before prescribing it. patients on the actual costs and benefits to using a drug. An article by Harold Pollack describes in detail the flaws in the provision of information by drug companies:

The pharmaceutical industry spends hundreds of millions of dollars every year advertising prescription drugs. About half of this is spent by company detailers, who promote products directly to doctors and pharmacists. As part of the sales pitch, detailers often treat doctors to lunch, or offer complementary trinkets, penlights, memo pads, or tickets to sporting events. Many doctors, struggling to keep current about all the new products and warnings, find detailers a convenient source for information about potential side effects and proper dosing of the medications they sell.

Detailing has attracted controversy due to a few well publicized scandals. A 1973 Senate investigation revealed that companies instructed detail men not to mention articles in medical journals that questioned the safety or effectiveness of the drugs that they sell.

More recently, a March 1989 PBS Frontline documentary, ′Prescriptions for Profit,′ claimed that detailers from McNeil Laboratories, a prominent drug maker, had misled doctors about dangerous side effects of Zomax, a lucrative new pain killer, during a $111 million sales campaign. The program presented

internal McNeil memoranda encouraging detailers not to discuss possible adverse reactions in their presentations to doctors, and to downplay these effects in conversation if the subject came up. Several patients died from anphulactic shock before the FDA forced Zomax′s removal from the market in early 1983.

Academic research lends credence to these concerns. A 1982 Harvard study examined physicians′ knowledge of commonly prescribed vasodilator medications for senile dementile and pain killers such as Darvon. Vasodilator therapy, advertised as a way to improve impaired cerebral blood flow, has no demonstrated therapeutic value. Similarly, despite marketing claims, clinical tests consistently find Darvon to be no more effective than aspirin for the relief of mild to moderate pain. The study found that, ′although the vast majority of practitioners perceived themselves as paying little attention to drug advertisements and detail men, as compared to the papers in the scientific literature, their beliefs about the effectiveness of the index drugs revealed quite the opposite pattern.′ Seventy-one percent of tested physicians agreed with erroneous claims found in vasodilator promotions, and thirty-two percent reported that they ′find cerebral vasodilators useful in managing confused geriatric patients.′ Forty-nine percent of the sample believed that Darvon is more effective than simple aspirin.[166]

This market failure based on asymmetrical information leads to excess demand for undesirable drugs because consumers and doctors will fail to demand

[166]Harold Pollack, Faculty Seminar on Truthfulness in Management sponsored by the Harvard Program on Ethics and the Professions, Harvard Business School, and the Kennedy School of Government, April 1989.

more desirable substitutes.

AIDS′ activists sudden objections to the FDA′s accelerated approval of AIDS drugs serve as an example of the problems associated with the approval of a drug before its costs and benefits are adequately demonstrated. The accelerated approval reduces substantially the amount of data that must be shown to the FDA before the FDA allows the marketing of the drug. In essence, the fast track approval system is a form of eliminating the FDA pre-market approval requirements for certain life threatening drugs. As reported by an August *15,* 1994 issue of Barrons:

Their [AIDS activists, some physicians, and even some drug companies] complaint is that AIDS drugs are coming to market in confusing profusion. Because testing has been done in a rush, full details about the new drugs′ side effects and basic effectiveness are unknown. The kind of data that have come out of these clinical studies is uninterpretable and ambiguous, charges [Derick] Link [representative of Gay Men′s Health Crises]. No one knows when to take them, how best to use them, or if the toxicities outweigh the benefit.[167]

Supporters of the proposal to end the requirement of FDA approval have failed to adequately address this problem of information disparities between drug companies and drug consumers. They have argued that imposing liability

[167]Edward A. Wyatt, *Rushing to Judgment,* BARRoN′S, Aug. 15, 1994 at 23.

on drug manufacturers will force drug companies to convey accurate information to the market concerning a drug's costs and benefits.[168] According to the argument, if strict liability was imposed on the drug manufacturers, the drug manufacturers would have to internalize all costs and benefits of their product. Therefore, it would be in their interests to make sure that patients would use the product only when the benefits to the patient outweighed the costs.

There are several responses to this argument. First, liability may provide drug companies with incentives to provide safety information, however it is not clear how liability will cause companies to disseminate information on effectiveness. While it may be easy for a patient who suffers serious side effects from a drug to sue for compensation, it would probably be extremely tough to recover against a drug company because the drug failed to cure a particular disease. Second, it is not clear what threshold of safety would have to passed before recovery would be allowed. A drug company would not be held liable for every side effect the drug causes because practically all drugs cause side effects. Therefore, there would have to be some threshold such as a severely debilitating side effect for a recovery. Such a threshold would dilute a company's incentives to produce information. Third, as emphasized throughout the paper, much of the drug industry is made up of small companies with practically no assets. Therefore, liability may do little to create incentives because the small companies producing drugs have little at stake. Fourth, as stated earlier, dissemination of

[168] *See* Usdin *supra* note 121.

information serves little purpose if doctors do not have the correct incentives to evaluate this information correctly. Therefore, unless doctors are instilled with the proper incentives to evaluate a drug′s costs and benefits properly, drug companies may find that it serves no purpose to disseminate accurate information. Also, if doctors fail to adequately evaluate the information, it is irrelevant that the drug companies produce the efficient amount of information. b. Delays in the production of information: Results in too much demand for drug products. Even if drug companies disseminate information on drugs they sell because this information will increase sales and reduce their liability. This information to a large extent will follow a drug′s introduction onto the market especially when the drug is introduced by a small biotechnology company. For example, a small biotechnology company with no current products or revenue facing financing problems which develops a drug with preliminary signs of safety and efficacy likely will introduce the product to the market and will continue with testing to generate more information about the drug. The danger with this system is that a drug is available to all American citizens without the availability of adequate information on its safety. Such a situation will inevitably result in another thalidomide-type tragedy.

c. Loss of confidence in the market for drugs: Results i too little demand for drug products. Another argument may be made against this proposal based on an entirely different view of the United States market for drugs following the implementation of this proposal. The removal of FDA drug approval requirements may create a state of considerable uncertainty in the U.S.

market for drugs. Doctors and patients may not be able to adequately evaluate the scientific merits of a particular new drug. Consequently, the demand for all new drugs may decline. Another result may be that drug consumers might demand only drugs manufactured by the large well established drug manufacturers based on the perception that these manufacturers produce safer products than the small biotechnology companies. Both of these outcomes negatively impact small biotechnology companies.

4. A better solution: deregulating early pre-clinical and clinical trials. granting drug companie right to export unapproved drugs. While I disagree with the proposal to undo FDA pre-marketing requirements, I do believe that certain changes must be made to the current drug approval process to reduce the cost of drug approval. As stated earlier, the heart of the problem faced by small biotechnology companies is that the drug review process is extremely costly and biotechnology companies with no products generate no profits to finance this process. Therefore, the cost of drug review must be reduced wherever possible. However, reductions in cost must only be implemented if their benefits outweigh their costs. Given this cost benefit analysis, I propose the following changes to the FDA drug approval process: (1) Pre-clinical regulations requiring preliminary evidence of a drug′s safety prior to the commencement of human trials should be eliminated; (2) Regulations designed to protect the safety of clinical subjects of early clinical trials should be eliminated; (3) Drug companies should be allowed to charge clinical test subjects; and (4) Drug export laws should be

modified so that U.S. biotechnology companies are granted greater freedom to export unapproved drugs to foreign countries.

a. Eliminating all pre-clinical regulations requiring preliminary evidence of a drug′s safety. Prior to human testing, extensive animal testing must be conducted to establish the safety of the drug for use in experimental groups. Following pre-clinical testing, an extensive IND application must be filed with the FDA which in addition to the testing takes considerable time to prepare.[169] It has been a common charge of the drug industry and commentators that these requirements are overly excessive based on the FDA′s continuing desire to place the protection of a small number of clinical subjects above the health of the entire United States population.[170] These large frontend costs associated with drug development substantially limit the number of drugs which small biotechnology companies may pursue and increase the risk of a biotechnology company′s failure. Therefore, eliminating these pre-clinical regulations will alleviate much of the cash crunch facing the biotechnology industry.

The benefits from eliminating these pre-clinical regulations outweigh the costs. First, extensive animal toxicity tests seem to serve little purpose. Twelve month studies do not appear to be necessary to determine toxicity in animals. According to the European scientific community, these animal toxicity tests produce few manifestations of toxicity after 3 months and no significant findings after 6 months.[171] Also, animal tests may screen out potentially safe and ben-

[169] *5ee supra* note 7.
[170] *5ee* Piercy *supra* note 33.
[171] Dillman *supra* note 4 at 928.

eficial drugs. For example, Sir Alexander Fleming claimed that penicillin is on the market today because it was never tested on animals.[172] Fleming has stated that had he known of penicillin's animal toxicity, he never would have tried it on humans.[173] Animal studies also often fail to reveal all of the potentially significant toxic effects of a drug in human beings. Some drugs that pose no side effects to animals may pose side effects to humans.[174] For example, a study of 6 chemically dissimilar drugs that had been tested extensively in rats, dogs and humans showed that animal testing failed to reveal more than fifty percent of the toxic effects in human beings.[175]

Second, drug manufacturers will conduct the efficient level of pre-clinical studies on a drug's safety. Investors will require preliminary evidence of a drug's safety and efficacy before they will finance human clinical studies. Also, drug manufacturers will have to compensate clinical subjects for the risk they bear. Test subjects will demand more money if the risks to their health are higher. Thus, manufacturers will have incentives to conduct pre-clinical tests to the extent that the marginal cost of further tests is less than the marginal value of the resultant reduction in risk. Strict requirements of informed consent will ensure that test subjects adequately evaluate the risks when deciding whether to enter into a drug study.

172 *Id.*
173 *Id.*
174 *Id.*
175 *Id.*

Third, my analysis of de-regulating pre-clinical trials differs from de-regulating the entire drug approval process because if a mistake is made fewer people are at risk. In Phase I and Phase II, no more than a couple of hundred volunteers are tested. Furthermore, upon discovery of a harmful side effect, a quick response can be made. Therefore, the use of an unsafe drug in these trials will have limited effects. On the other hand, an unsafe drug released onto the U.S. drug market could reach millions of people and removing the drug from the market may be extremely difficult.

b. Eliminating early clinical regulations designed to protect the safety of clinical subjects. My justifications for this proposal are the same as for the above proposal. As I have stated earlier, one of the major problems faced by small biotechnology companies is the excessive caution of the FDA during early clinical trials. Drug companies have recommended reasonable risk levels in early clinicals.[176] However, the FDA's response has been to suggest increased dose levels, lengthy observation periods and countless meetings with the FDA to discuss the safety to clinical subjects.[177] As in the above proposal, I believe that the risks are minimal and can be justified by the substantial benefits of decreasing the cost of drug approval for small biotechnology companies.

c. Allowing drug companies to charge their clinical test subjects. I propose that current FDA regulations should be changed to allow drug companies to charge their test subjects for the experimental treatment they receive. Cur-

[176] Piercy *supra* note 33.
[177] *Id.*

rently, the FDA does not allow drug companies to charge for Investigational drugs except under certain exceptions for drugs that treat life threatening illnesses. The current rule against charging for experimental drugs actually discriminates against small biotech companies in favor of the large pharmaceutical companies. Large pharmaceutical manufacturers with millions of dollars in sales revenues are able to finance the drug experimentation process. However, small biotechnology companies who have no current income and are not allowed to recover their drug development costs by charging their patients are often driven out of the market or are forced to sell their technology to the larger companies. Allowing small biotechnology companies to charge their patients would remedy this situation.

Furthermore, allowing drug companies to charge for clinical trials would supplement my proposal to deregulate pre-clinical trials and early clinical trials. Allowing drug companies to charge would provide these companies with an added incentive to prove that their drug has limited risks.

Several arguments against this proposal can be anticipated. First, allowing companies to charge for unapproved drugs decreases the incentive for companies to get approval for unapproved drugs. However, the FDA might limit the price that can be charged for experimental drugs or the FDA might limit the size of the clinical group. Either action will give drug companies ample incentives to obtain drug approval. Second, how can drug companies charge their test subjects in a blind experiment where some of the patients

receive a placebo? In response, drug companies may charge all of the test subjects up front but then grant refunds to those who received the placebo. Another solution would be to charge all of the patients an average cost for the testing and patients would be subject to the risk that they must pay for the placebo. Both of these solutions are even more workable given insurance markets. d. Modifying the current drug export laws to expand the ability of drug companies to export unapproved drugs. The current unapproved drug export laws should be modified to give U.S. drug companies greater ability to sell unapproved drugs to foreign markets. I agree with a February 27, *1995* press release by Biotechnology Industry Organization (BIO) calling for modifications to current U.S. export laws reducing restrictions on the exportation of innovative drugs to patients in other countries.[178]

Currently, the right to export unapproved drugs to foreign countries is limited. Exports of most unapproved drugs and biologics are limited to 21 countries listed in section 802(b)(4)(A) of the Federal Food, Drug and Cosmetic Act.[179] Shipment of unapproved drugs to unlisted countries is expressly prohibited˜ For a drug to be eligible for export, the drug must be the subject of an IND and U.S. marketing approval for the drug must be actively pursued.[180] Also, the drug must be approved for marketing in the country receiving the drug.[181]

[178]Biotechnology Industry Organization, *FDA Reform. Achievable Steps to Improve Access to New Therapies and Cures,* Feb. 27, 1995.
[179]Jeffrey N. Gibbs, *Movement of biotechnology-Derived Products Exports, Imports and Transit,* 256 PLI/PAT 33 (1988).
[180]*Id.*
[181]*d.*

Restricting exports to 21 approved countries and requiring an approved IND prior to export protects foreign countries at the expense of the U.S. biotechnology industry. These restrictions on exports impede the growth of the U.S. biotechnology industry. The restrictions have two effects. First, biotechnology companies developing new drug products are denied a source of financing. Second, the restrictions encourage biotechnology companies to build plants over seas in foreign countries that desire the new drug products but are unable to get them because of the U.S. export restrictions. As stated earlier in this paper, the movement of biotechnology companies to foreign countries is particularly troublesome for the U.S. biotechnology industry. Modifying current U.S. export laws to expand the right of biotechnology companies to export unapproved drugs will alleviate these problems. As stated by BIO in a Feb. 27, *1995* press release:

The biotechnology industry developed from scientific advances made in this country. Permitting the exportation of innovative products to patients in other countries will retain the fruits of this investment.[182]

VII. CONCLUSION

The United States has one of the most sophisticated drug approval systems in the world. This intricate system, directed by the FDA, has generated

[182]Biotechnology Industry Organization *supra* note 178 at 2.

considerable confidence in the safety and effectiveness of marketed drugs. However, the United States′ system of drug approval entails exhorbitant costs which have adversely affected the infant biotechnology industry. Small biotechnology companies, unable to generate sufficient funds to finance the drug approval process, face possible extinction. The potential decline of small biotech companies threatens innovative drug development and the United States′ reign as a global leader in biotechnology. Therefore, the United States would benefit from changes in the current FDA drug approval process that would prevent the decline of small biotechnology companies without endangering the safety and effectiveness of the drug supply. In this paper, I have attempted to analyze some of the current proposals to change drug approval as to their ability to solve this problem. I have also presented my own proposals which I believe will benefit biotechnology companies without imposing unnecessary risks on the U.S. population.